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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/007,078 | 11/08/2001 | Donna T. Ward | RTS-0236 | 6940 |

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| EXAMINER | |
|---|---|
| SCHULTZ, JAMES | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | 14 |

DATE MAILED: 08/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FSU

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/007,078 | WARD ET AL. | |
| | Examiner | Art Unit | |
| | J. Douglas Schultz | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-15,20-24 and 26-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-15, 20-24, 26-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Status of Application/Amendment/Claims*

1. Applicant's response filed June 6, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed February 7, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Response to Arguments*

3. Claims 15, 20-24, 26-28, and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of EIF2C1 expression in vitro, does not reasonably provide enablement for *in vivo* antisense-mediated modulation of an endogenous RNA-mediated interference pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Claims 15, 28, and 30 are hereby included in this rejection of record insofar as they are also drawn to methods of using the instantly claimed compounds *in vivo*. This rejection is repeated for the same reasons of record as set forth in the Office action mailed May 7, 2002.

In addition, the reference of Agami (Curr. Opin. Chem. Biol. 2002, v6:829-834) is newly cited to demonstrate that the art cited previously in support of the lack of enablement directed to

the use of antisense compounds *in vivo* is also considered to be applicable to the methods of claims drawn to RNAi. Although the cellular mechanisms of antisense oligonucleotide inhibition *in vivo* of claims 15, 26 and 27 may differ from the cellular mechanisms of RNAi-mediated *in vivo* use as claimed in claims 20-24, Agami indicates that the compounds used in both methods are nucleic acid oligos, and accordingly, that applications involving RNAi may be considered to follow the existing paradigms already in place for those utilizing antisense strategies (see last para. p. 832), and thus subject to the same unpredictabilities as outlined in previous Office actions.

Applicants have traversed the above rejection on the assertion that the instant specification provides one of skill in the art with all the tools necessary to practice the invention as claimed *in vivo*, and that the Office mischaracterized the references of Crooke et al ("Crooke")., and Gewirtz et al. ("Gewirtz"), which were cited to support the unpredictability of using results from *in vitro* studies to predict *in vivo* results.

In particular applicants assert that the citation of Crooke et al., who states that "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate....one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies" does not actually discuss whether a cell will take up any oligo. Applicants disagree with the examiner's reasoning out that based on this passage, one cannot determine whether an oligo taken up by a cell *in vitro* will be similarly taken up *in vivo*, even if the *in vitro* assay showed target inhibition. Applicants argue that the passage does not even discuss *in vivo* uptake, and that while there may be some difference between *in vitro* and *in vivo* uptake, that Crooke does not indicate that no uptake will occur.

Applicants arguments are not convincing, because as applicants concede, uptake is one parameter of pharmacokinetics; since the Crooke passage clearly refers to and discusses *in vitro* uptake, then proceeds to state that one cannot predict *in vivo* pharmacokinetics from *in vitro* results, one parameter of which is uptake, one of skill in the art would understand that *in vitro* uptake not correlate with *in vivo* uptake. It would be difficult to read anything else from Crooke's passage. Furthermore, applicants contention that Crooke "does not teach that the compounds will not be taken up *in vivo*" is not the proper analysis for enablement, as no requirement exists to prove a negative, i.e. that no uptake will occur; rather the test is whether such uptake is predictable or not. As argued above, Crooke is considered to support the presence of such unpredictability.

Applicants further argue that the passage of Gewirtz that discusses the use of a transfection agent that works well *in vitro* but needs to be studied more *in vivo* is not relevant, because applicant is not claiming the use of a transfection agent. However, the passage was cited to underscore the problems associated with uptake and trafficking, such as those referenced by Gewirtz as he states: "[t]he other major problem is this field is the ability to deliver ODN [i.e. oligodeoxynucleotides] into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient." GS2888 is discussed as potential solution to this problem that has worked *in vitro*, but for which "several caveats should temper our enthusiasm"; namely that it is not known how cells *in vivo* would respond to such a compound. This again supports the unpredictability of uptake. Finally, in opposition to applicants comments that Gewirtz was mischaracterized, Applicants are pointed to statements directly from Gewirtz that "[t]o the extent that many have tried to use AS ODNs [antisense] and

more than a few have been frustrated by results that were noninformative at best--or even worse, misleading or unreproducible-- it is easy to understand why this approach has become somewhat controversial", and also that "[t]he antisense approach has generated controversy with regard to mehcanism of action, reliability, and ultimate therapeutic utility." While Gewirtz does indicate the high potential of the field, such comments are always framed in the context of potential, not what is predictable. In light of the problems known to those of skill in the art and raised in previous Office actions, such "potential" for therapeutic utility is considered to be quite distinct from its predictability. For these reasons, both Gewirtz and Crooke are considered to indicate unpredictability in the use of *in vitro* results as applied to *in vivo* use.

Significantly, applicants have not presented any arguments at all regarding the three other review paper cited in the previous Office action in support of applicants lack of enablement.

Applicants have submitted 7 primary research references that teach varying degrees of success attained in the use of antisense oligos *in vivo*. Of these, the teachings of Smith and Dwyer are not considered relevant, because the enablement rejection is based on the unpredictability of using *in vitro* results to predict *in vivo* inhibiton, and neither Smith nor Dwyer teach *in vitro* inhibition using their respective oligos. Of the remaining 5, all experiments were performed in severely immuno-compromised mice. Since one of the cited issues remaining to be resolved in the field is that most injected oligonucleotides stimulate a disproportionately high non-specific immune response in mammals, the use of severely immuno-compromised mice is not considered to represent what happens in wild-type mammals.

Furthermore, even if all the details of applicants' cited studies matched the limitations of applicants' claimed invention, which they don't, the fact that some success has been reported in

translating *in vitro* results to an *in vivo* environment does not provide convincing evidence that such *in vivo* results are predictable from *in vitro* studies in general, because none of the references teach how to circumvent previously cited and art-recognized problems in the field relating to cellular and target access, immune reactions, and non-specific interactions with endogenous proteins. It is maintained that these articles do not provide the guidance necessary to overcome the cited obstacles that remain in the field of oligonucleotide-mediated treatment or *in vivo* gene inhibition, because the results from these single sets of experiments, performed in organisms not found in nature, do not outweigh the multitude of art reviewed in the 5 review articles provided and cited in previous Office actions. Thus, the primary research articles cited showing some success in individual trials, is not considered to accurately portray the state of the art of using *in vitro* results to predict *in vivo* success as a predictable art. Accordingly, one of skill would have to engage in trial and error experimentation to practice applicants' claimed invention.

Applicants also argue that the absence of working models does not preclude the enablement of their invention, and that the enablement requirement is different from the considerations made by the FDA for drug approval. Applicant is reminded that no such requirements analogous to those mandated by the FDA have ever been imposed, nor is one being imposed now. Furthermore, while it is true that the absence of working models does not preclude enablement, it is nevertheless an important factor considered when weighing enablement, and is given particularly high weight when determining the enablement of an invention in an unpredictable art. As pointed out above and in every previous Office action, extrapolating from *in vitro* results to *in vivo* success is considered to be an unpredictable art.

Applicants finally argue that the references are silent on the subject of *in vivo* results, and that "the absence of a positive result is not evidence of a negative result". In response, it is maintained that considered as a whole, the references cited indicate that *in vitro* results to not predictably indicate *in vivo* success for reasons given in previous Office actions. Applicants reference to the absence of a positive result in the examiner-cited prior art places a substantial burden on the specification to provide adequate enabling disclosure. As has been set forth in previous Office actions, applicants disclosure of the inhibition of a gene in cell culture is not considered to be representative of inhbition in the complex internal milieu of the whole animal, and therefore not considered an analogous model system. See the five review articles cited and passages referenced therefrom in the 35 U.S.C. § 112 1st paragraph enablement rejection in the Office action mailed February 7, 2003.

***Claim Rejections - 35 USC § 102/103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 and 103 that form the basis for the rejections under these sections made in this Office action:

> A person shall be entitled to a patent unless –
>
> 102(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> 102(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

> 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 2, 12 and 14 are rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or obvious by Koesters et al. (of record).

The claims of the above invention are drawn to antisense compounds 8 to 50 nucleotides in length that specifically hybridize with and inhibit the expression of EIF2C1 of SEQ ID NO: 3.

The primers used by Koesters et al. in the isolation of EIF2C1 possess 100% identity with the instant target of SEQ ID NO: 3, and would thus specifically hybridize with said target. Further explanation is provided below.

5. Claims 1, 2, 12 and 14 are rejected under 35 U.S.C. 102(e) and 103(a) as being anticipated and/or obvious by Schalling et al. (U.S. Patent Number 5,695,933).

The claims of the above invention are drawn to antisense compounds 8 to 50 nucleotides in length that specifically hybridize with and inhibit the expression of EIF2C1 of SEQ ID NO: 3.

SEQ ID NO: 11 of Schalling et al. is 30 nucleotides long and hybridizes to nucleotides 7413-7435 of applicants instant target. In view of applicants definition of "specifically hybridizable" on page 10 beginning at line 24 wherein an oligo is considered to specifically hybridize if a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs, and because 8 out of 30 nucleotides match the target region identified above with 100% complementarity, the oligo of Schalling would thus specifically hybridize with said target.

Although the references of Koesters et al. and Schalling et al. do not specifically teach the function of inhibiting applicants' instant SEQ ID NO: 3 as claimed in the present application, the above-listed compounds meet all the structural limitations as set forth in the instant claims. Because the sequences are substantially identical to applicant's claimed compounds, in the absence of evidence to the contrary said compounds are thus considered to possess the functional limitations of specifically hybridizing with and inhibiting the expression of applicants' instant SEQ ID NO: **3**. Support for this conclusion is drawn from MPEP 2112:

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim **but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection**. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims. *Emphasis supplied.*

In rejecting the claims of the above under 35 U.S.C. 102 and 103, a prima facie case has been established by the examiner whereby the burden of proof in showing that the claimed

compounds are not anticipated by the compound(s) of the prior art as stated lies with the applicant, as per MPEP 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Thus, in the absence of evidence to the contrary, the antisense compounds of claims 1, 2, 12 and 14 of the instant application are considered anticipated and/or obvious as outlined above.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Fire et al. (Nature, 1998 v391:806-811).

The invention of the above claims is drawn to a method of interfering with a function of RNA in a cell comprising contacting a cell with an antisense compound capable of modulating an endogenous RNA-mediated interference pathway, wherein said function may be protein translation, or wherein said compound is an antisense oligonucleotide compound.

Fire et al. teaches a method of interfering with a function of RNA in a cell comprising contacting a cell with an antisense compound capable of modulating an endogenous RNA-

mediated interference pathway, wherein said function may be protein translation, or wherein said compound is an antisense oligonucleotide compound.

***Claim Rejections - 35 USC § 103***

Some of applicant's arguments with respect to claims 1, 2, and 4-15 have been considered but are moot in view of the new ground(s) of rejection. Those arguments considered to be relevant to the rejection as amended below are addressed following said amended rejection.

Claims 1, 2, 4-15, 20, 24 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koesters et al., in view of Cikaluk et al. (Mol. Biol. Cell, 1999. v10:3357-3372), Taylor et al., Baracchini et al., and Milner et al.

The invention of the above claims is drawn to antisense compounds that target EIF2C1 of SEQ ID NO: 3, or said compounds comprising internucleoside, nucleobase, and 2' modifications, chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents thereof, and compounds that inhibit by at least 60% or 80%.

Koesters et al. teach the nucleotide sequence encoding EIF2C1 (abstract, Fig. 1, and GenBank accession number AF093097). Koesters et al. do not teach antisense oligonucleotides that comprise internucleoside, sugar or nucleobase modifications, or chimeric antisense molecules, nor methods of inhibition using antisense oligos.

Cikaluk et al. teach antisense (RNAi)-mediated inhibition of GERp95, the C. elegans orthologue of applicants instant EIF2C1 target of SEQ ID NO: 3.

Taylor et al. teach the use of antisense oligos to inhibit any gene of known sequence as a research tool for the elucidation of gene function. Taylor et al. teach that using modern software screeing programs and high-affinity chimeras, one of ordinary skill in the art would have to screen only 3-6 oligos in order to generate one that inhibits 66-95%.

Milner et al. teach the screening of antisense oligonucleotides for their ability to inhibit a target gene of known sequence in vitro (See entire document).

Baracchini et al teach chimeric antisense as well as internucleoside, sugar or nucleobase modifications (column 6, line 18-column 8, line 56).

It would have been obvious to one of ordinary skill to design and use antisense molecules for the specific inhibition of EIF2C1 expression, since the sequence for EIF2C1 was taught previously by Koesters et al., and since Taylor et al. teach that antisense oligonucleotides can be designed to inhibit any gene of known sequence. One of ordinary skill in the art would have been motivated to inhibit EIF2C1 because Koesters et al. found that elevated expression of EIF2C1 has been found in tumors harboring a mutation in the Wilms tumor suppressor gene (page 248, para. 2, lines 13-17), and because Taylor et al. teach that such antisense inhibition is valuable as a research tool to elucidate gene function. Cikaluk et al. teach further motivation to make antisense/nucleic acid based inhibitors to inhibit the instant EIF2C1 target by expressly teaching the antisense/RNAi-mediated inhibition of the C. elegans orthologue of EIF2C1, i.e. GERp95, which indicates the desirability of determining the function of EIF2C1, and that one of ordinary

skill would have had a reasonable expectation of success in making and using the instantly claimed compounds.

Moreover, one of ordinary skill in the art would have had a reasonable expectation of success of finding antisense sequences that inhibit EIF2C1 expression, because the methods for screening such antisense molecules had been taught previously by Milner et al. Furthermore, one of ordinary skill in the art would have been motivated to incorporate internucleoside, sugar and nucleobase modifications into such antisense molecules because it had been taught previously by Baracchini et al. that such modifications enhance antisense stability and cellular uptake. One of ordinary skill in the art would have expected that the incorporation of such modifications into antisense molecules would render them less susceptible to nuclease degradation, as taught by Baracchini et al. Finally, because Taylor et al. teach that with modern software screening programs and high-affinity chimeras, one of ordinary skill in the art would have to screen only 3-6 oligos in order to generate one that inhibits 66-95%, thus meeting the limitations of added claims 28-31.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants argue that there is no motivation to combine the instant references. Applicants argue that "an obvious to try standard" has been employed, and finally that a person of ordinary skill would have had to pick and choose from the various elements of the cited references to produce the claimed invention.

In response to the allegation that no motivation exists in the prior art to use antisense to target EIF2C1 as claimed by applicants, it is responded that the broad claim language of claim 1, whereby any compound is encompassed that hybridizes with and inhibits EIF2C1 of SEQ ID NO: 3, is indeed obvious under 35 U.S.C. § 103(a). Motivation is provided from multiple sources, primarily Taylor et al. and Koesters et al. Taylor et al. explicitly states (pg. 562, 1st para. of Intro.) that due the specificity and ease of antisense targeting, that antisense oligos are attractive candidates as therapeutic agents and as research tools to investigate gene function. Taylor et al. also state in the same paragraph that antisense oligos of the length claimed by applicants can be designed to inhibit any gene target provided the sequence is known. Taylor et al. underscore the specificity and ease of use statement by citing that with modern software screeing programs and high-affinity chimeras, one of ordinary skill in the art would have to screen only 3-6 oligos in order to generate one that inhibits 66-95%. That antisense oligos are considered routine tools for gene inhibition of known sequence is important when understanding the teachings of Koesters et al.

According to Koesters et al. on page 217 (last paragraph) the instant target of EIF2C1 is homologous with other proteins and is also overexpressed in Wilms tumors, all of which makes "human EIF2C1 an interesting candidate for potential involvement in Wilms tumorigenesis". Since Taylor et al. teach that antisense specificity and ease of use make them attractive for elucidating gene function, and because one of ordinary skill would want to elucidate the function of a gene with a proposed role in tumorigenesis, it is maintained that one of ordinary skill would be motivated to make a compound that meets the broad claim limitations set forth by applicant to investigate the function of the instant target EIF2C1. Furthermore, both Taylor et al. and

Baracchini et al. describes methods by which to make and use modified antisense molecules, wherein said modifications provide a longer half-life, greater cell membrane penetration, and greater target binding capacity than standard oligonucleotides. Since one of ordinary skill in the art would consider longer half-life, greater cell membrane penetration, and greater target binding capacity to be desirable attributes of an inhibitory compound, one of ordinary skill would have been motivated to make such modified oligo compounds.

Further evidence that one of ordinary skill would have been motivated to inhibit the instant target is provided by Cikaluk et al., who expressly teach antisense/RNAi-mediated inhibition of the C. elegans related orthologue, GERp95.

Applicants argue that the motivation above provides merely for an "obvious to try" situation, since the motivation to combine references arises because the subject matter of the claimed invention is a promising field for experiementation, and that the prior art only gives general guidance as to the particular form of the claimed invention in how to achieve it. This is not considered convincing, because Taylor et al. indicate that antisense inhibition is routine to those skilled in the art as evidenced by the above referenced statement regarding specificity and ease of use. Furthermore, Baracchini et al. provides detailed, step by step instructions in how to make and use such antisense molecules. Therefore, since one would be motivated to investigate the role of EIF2C1 in Wilms tumorigenesis, and since Taylor et al. teaches that sequences genes can be inhibited using antisense technology that is routine to one of ordinary skill, and finally because Baracchini teach step by step instructions on how to accomplish antisense-mediated gene inhibition, the guidance is not general at all, but rather very specific. As evidence, applicants are directed to examples 1 through 3 of Baracchini, which demonstrate how to mix the

precursors of individual nucleotides to make modifed oligos, how to transfect said oligos into cells *in vitro*, and how to harvest the cells and run ELISA's on the resulting homogenates to check for inhibition among other things. The level of detail provided includes the concentration of all reagents used, times of incubation, temperatures used, even manufacturers of various supplies required. Thus, the teachings are not general, and thus don't fit applicants description of an "obvious to try" situation.

Finally, applicants argue that if the examiner's reasoning were carried to its logical end, that no antisense sequences would be considered non-obvious if a particular target was known. This is simply not true, because there are many genes for which no motivation to inhibit exist, unlike the instant target, which has been implicated in tumorigenesis. Furthermore, one of ordinary skill in the art would understand from the teachings of Taylor et al. or Baracchini et al. that each antisense sequence has its own efficacy and ability to inhibit its target. Thus, the teachings of Taylor et al., and/or Baracchini et al. would not lead one of skill in the art to any one particular individual antisense sequence. Applicants are reminded that the instant claims are not drawn to any one particular one particular individual antisense sequence, but rather to the entire genus of any antisense sequences that binds to to and inhibit the instant target of EIF2C1 of SEQ ID NO: 3.

Applicants also argue that each reference, when looked at individually, does not teach or suggest compounds 8 to 50 nucleotides long that target the instant SEQ ID NO: 3, wherein said compound specifically hybridizes with and inhibits the expression of EIF2C1.

However, the claims have not been rejected under 35 U.S.C. § 102, but rather under 35 U.S.C. § 103(a). Thus, the proper test is not whether each reference teaches the invention

individually, but rather whether what their combined teaching would have suggested to one of ordinary skill in the art at the time the invention was filed. Contrary to applicants' assertion, motivation to combine the references was set forth in the Office action dated May 7, 2002, and is provided both by Koesters et al., who teaches that the claimed target is upregulated in specific tumor cells, making it an attractive candidate for inhibition, and by Taylor et al. who teach that antisense inhibition is a preferred mechanism for studying the function of genes, and that antisense molecules can be generated against any target of known sequence. For these reasons the instant rejection of record is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
August 18, 2003

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600